GLOBAL VACCINE SAFETY BLUEPRINT 2.0 BACKGROUND RESEARCH

July 2019

Prepared by Deloitte Consulting LLP

World Health Organization

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WHO/MVP/EMP/SAV/2019.03

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Acronyms

AE: adverse event

AEFI: adverse event following immunization

AFRO: Regional Office for Africa

CIOMS: Council for International Organizations of Medical Sciences

EMRO: Regional Office for the Eastern Mediterranean

EPI: Expanded Programme on Immunization

EURO: Regional Office for Europe

GACVS: Global Advisory Committee on Vaccine Safety

GVAP: Global Vaccine Action Plan

GVSI: Global Vaccine Safety Initiative

HPV: human papillomavirus

ICH: International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ITAGs: Immunization Technical Advisory Groups

LMICs: low and middle-income countries

NGOs: non-governmental organizations

NRAs: National Regulatory Authorities

PAHO: Pan American Health Organization/ Regional Office for the Americas

PBRER: Periodic Benefit-Risk Evaluation Report

PMS: post marketing surveillance

PPI: public-private information

PV: pharmacovigilance

SDGs: Sustainable Development Goals

SEARO: Regional Office for South East Asia

UHC: universal health coverage

WHO: World Health Organization

WPRO: Regional Office for the Western Pacific

Executive Summary

In 2012, the Global Vaccine Action Plan (GVAP) for 2011-2020 was endorsed by 194 Member States at the World Health Assembly, serving as a framework to guide immunization efforts through 2020. The Global Vaccine Safety Blueprint was created alongside GVAP to set objectives for building the capacity of vaccine safety in low and middle-income countries (LMICs) to better detect, report, and analyse adverse events. As the GVAP comes to an end in 2020, the World Health Organization (WHO) is working with stakeholders to develop a new framework, Immunization Agenda 2030, in the context of the Sustainable Development Goals (SDGs) and the changing immunization landscape. This serves as an opportune time to also evaluate the impact and strategic direction of the Global Vaccine Safety Blueprint and its implementation mechanism, the Global Vaccine Safety Initiative (GVSI). For that purpose, background research was conducted in 2019 to obtain input from vaccine safety experts, national regulatory officials, immunization program managers, global agencies, industry, non-governmental organizations (NGOs), and others.

This report serves to synthesize the findings of that research and provide recommendations for the drafting of the Global Vaccine Safety Blueprint 2.0. Information collected from more than 200 stakeholders that work in vaccine safety indicated that many of the challenges discovered during the creation of the first Global Vaccine Safety Blueprint in 2011 remain. Additionally, new challenges related to hesitancy and emergencies have arisen, along with opportunities to focus the next iteration of the Blueprint.

Persisting and Emerging Challenges

Since the development of the Global Vaccine Safety Blueprint and GVSI, **vaccine safety capacity has improved significantly in LMICs**, in part due to the creation of tools and methods to assist with pharmacovigilance (PV) and additional efforts undertaken by countries to strengthen vaccine safety systems.

While capacity has improved, **many of the same challenges from Blueprint 1.0 persist**. These challenges include: low detection and reporting; investigation of safety signals; epidemiologic methods for active surveillance; lack of clarity in roles and responsibilities at the country level for National Regulatory Authorities (NRAs), Expanded Programmes on Immunization (EPIs) and industry; and a need for more information-sharing between countries.

With reference to the next Blueprint, respondents highlighted the **necessity of addressing vaccine hesitancy** and of understanding the distinction between real and perceived vaccine safety concerns among the general public, noting that these challenges are becoming a consistent part of the vaccine landscape. Better vaccine safety data will assist with addressing this emerging challenge, but many respondents also noted the importance of using social networks as a tool to share scientific and accurate vaccine safety information to proactively combat the rise of misinformation. Stakeholders noted that it is critical to **empower consumers with scientific information and the risks and benefits** of vaccines to build vaccine confidence.

As the world faces an increasing number of ongoing conflicts, disease outbreaks and other emergencies, stakeholders would like to see these emerging challenges for vaccine safety addressed in Blueprint 2.0. This can include providing guidance to monitor vaccine safety in conflict and low-resourced settings in addition to managing crisis communications during an outbreak. **Ensuring support for vaccine services, including vaccine safety, in acute and chronic emergencies** will be an area of importance for overall immunization efforts.

Focusing the Blueprint

The eight strategic objectives in Blueprint 1.0 aimed to cover all aspects of vaccine safety. In Blueprint 2.0, stakeholders recommend selecting a **few key priorities for the next decade to maximize impact**. This process will be particularly important, as the Immunization Agenda 2030 aims to be an overarching framework rather than an articulation of priorities. A few vaccine safety priorities suggested by respondents include communications focused on vaccine safety, better engagement with industry, and the development of guidance and technical support for reporting, causality assessment, and monitoring of pregnant women.

In line with the Immunization Agenda 2030 framework, stakeholders would also like to see a **greater focus on country ownership** in Blueprint 2.0. WHO and its partners can support country ownership by playing a larger role in advocacy with national governments and assisting with the creation of regulatory networks, on adverse events following immunization (AEFI) committees and other bodies to support national vaccine safety capacity and ownership.

Stakeholders support Blueprint 2.0's taking a broader focus beyond LMICs, but it will be important to **outline objectives for countries not just by income level but also by critical benchmarks of vaccine safety maturity, including surveillance capabilities, regulatory framework, and confidence**. For example, many low-income countries often need to prioritize foundational PV capabilities while many high-income countries are facing a rise of vaccine hesitancy and thus need more support around risk communications. These unique needs should be addressed with responses tailored accordingly.

Roles and Accountability

Stakeholders view WHO as a leader and convener in vaccine safety, but this role does not exist in a vacuum.

Blueprint 2.0 should **outline the critical roles and engagement needed** of other global, regional and country stakeholders, as well as those at the local level - health workers, clinician associations, patients, and civil society -- to maximize impact through partnerships and outreach.

Finally, the need for an accountability framework to measure progress towards Blueprint 2.0 goals is clear. However, **harmonization of vaccine safety data and methods across countries will be an important step to comprehensively measure progress**. Regional and global harmonization initiatives face funding, infrastructure and political challenges, but stakeholders still want to see these initiatives pushed forward.

Section I: Introduction

Background

As Immunization Agenda 2030 takes shape, it is necessary to evaluate the current vaccine safety landscape in order to develop key vaccine safety priorities for the next decade. The purpose of this background research is to assess the impact of emerging trends in vaccine safety and immunizations more broadly and to synthesize stakeholders' inputs related to vaccine safety needs and priorities for the next decade.

To accomplish this aim, two surveys were sent to 352 vaccine safety stakeholders across a number of stakeholder groups, including government staff from both EPI and NRAs, global agencies, vaccine manufacturers, donors, researchers, and other vaccine safety experts. (For more information on the survey methods and respondents, please refer to the Appendix). A small number of stakeholders also participated in follow-up interviews to provide additional context and insights regarding their feedback. These surveys and interviews were designed to address several key objectives prior to the drafting of Blueprint 2.0, including the following:

- understand **stakeholders' awareness of Blueprint 1.0 priorities and activities**, as well as **seek input on future priorities and activities** to inform Blueprint 2.0
- understand stakeholders' **perception of Blueprint 1.0 impact** to date
- understand **stakeholders' views on the current threats** facing vaccine safety, and **how they can be addressed using Blueprint 2.0**
- pinpoint **capacity improvements** (at the country and international level) for detecting, reporting, investigating, analyzing, and communicating adverse events (AE) since last landscape analysis conducted in 2011
- identify **additional improvements needed** (at the country and international level) to improve capacity for detecting, reporting, investigating, analysing, and communicating AEs
- identify **areas for collaboration** across stakeholders, and **better understand current roles and responsibilities** of manufacturers, regulators, EPI program staff, international and non-profit groups and other vaccine safety stakeholders

In total, 208 respondents (59%) began the survey and 148 fully completed it (42%), providing critical expertise and insights related to these objectives.

Context of Blueprint 1.0 and the Creation of GVSI

Following the landscape analysis conducted in 2012, the Global Vaccine Safety Blueprint 1.0 was developed with a core set of strategic goals and objectives to implement those goals.

Blueprint 1.0

Mission: To optimize the safety of vaccines through effective use of pharmacovigilance principles and methods

Vision: Effective vaccine pharmacovigilance systems are established in all countries

Overarching Goals:
- To assist **LMICs to have at least minimal capacity** for vaccine safety activities
- To **enhance capacity for vaccine safety assessment** in countries that introduce newly developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines
- To **establish a global vaccine safety support structure**

Section I: Introduction

Blueprint 1.0 proposes eight complementary implementation objectives. Four of these objectives aim to improve the technical aspects of spontaneous reporting, active surveillance and risk communication and to ensure the availability of harmonized methods and tools. The remaining four objectives promote the establishment of effective managerial principles to facilitate international collaboration and information exchange relating to vaccine safety monitoring. Implementing the Blueprint is a task that requires coordinated participation of vaccine safety stakeholders worldwide.

8 Implementation Objectives of the Global Vaccine Safety Blueprint 1.0

Investigation of Safety Signals: To strengthen the ability of countries to investigate vaccine safety signals

Vaccine Safety Communication: To develop vaccine safety communication plans at country level

AEFI Detection: To strengthen vaccine safety monitoring in all countries

Tools and Methods: To develop internationally harmonized tools and methods to support country vaccine safety activities

Public-Private Information Exchange: To put in place systems for appropriate interaction between national governments, multilateral agencies, and manufacturers

Regulatory Framework: To promote a legal, regulatory and administrative framework for the safety of vaccines at national, regional and international levels

Global Analysis and Response: To provide expert advice on vaccine safety issues at national, regional and international levels

Technical Support and Trainings: To strengthen regional and global technical-support platforms that meet countries' expressed needs

These eight objectives directed the priorities and activities of the GVSI. As part of this background research, stakeholders provided feedback on their awareness of the GVSI's support in these areas, the perceived utility of the GVSI's support in these areas, and any other areas they recommended be prioritized over the next decade.

To support these objectives, WHO launched the GVSI in March 2012. The GVSI provides the framework for WHO to convene its member states and partners to further implement the Blueprint strategy. Using the eight implementation objectives laid out in Blueprint 1.0, the GVSI maintains a portfolio of activities and holds regular meetings to convene global vaccine safety stakeholders.

The Changing Landscape

The GVAP guided global vaccine and immunization efforts from 2011 to 2020. Describing the immunization landscape, the GVAP also laid out six strategic objectives and was accompanied by performance measures to track progress towards achieving these objectives. The development of Blueprint 1.0 aligned closely with the overarching objectives of the GVAP, with its own set of strategic objectives for vaccine safety within the broader goals for immunization

Beginning in 2020, Immunization Agenda 2030 will serve to drive the next decade of vaccine and immunization efforts. While the Agenda is still in draft, it prioritizes areas such as equity and access, fragility and emergencies, sustainability and accountability by ensuring that approaches are people-focused, and country and data-driven, and that they also utilize partnerships. As humanity is confronted by high-profile pandemics, ongoing conflicts, and anti-vaccine lobbies in this new landscape, the ability of immunization programs to safely deliver and monitor their vaccines needs to be adapted accordingly. Therefore, developing a specific vaccine safety approach to the rapidly changing world of immunization is critical to ensure that the right priorities- plans, strategies, and activities are in place to address the emerging issues. These are areas that can be addressed as the Blueprint is re-evaluated and updated for the next decade.

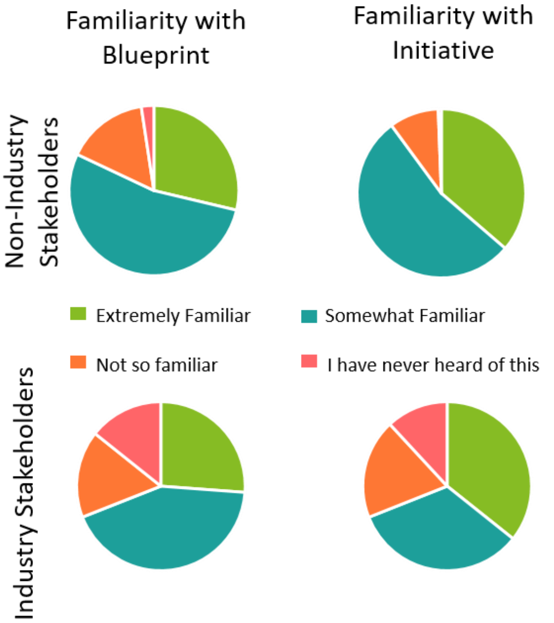
WHO's five-year plan to help build effective and efficient regulatory systems, Delivering Quality-Assured Medical Products for All 2019 - 2023, will also serve as a key roadmap for the next Blueprint and future vaccine safety activities. This plan is designed to help national regulators protect the public, enable access, and encourage innovation in medical products, which includes medicines, vaccines, in vitro diagnostics, medical devices, and other products. This regulatory strengthening plan lays out four strategic priorities:

1. strengthen country and regional regulatory systems in line with the drive towards UHC
2. increase regulatory preparedness for public health emergencies
3. strengthen and expand WHO prequalification and product risk-assessment processes
4. increase the scope and impact of WHO's regulatory support activities

Strengthening national and regional regulatory systems, particularly in the context of crises and emergencies, is an essential part of vaccine safety and was highlighted by many stakeholders as a priority in the next decade. This plan can help the GVSI and Blueprint 2.0 align with broader regulatory strengthening efforts across WHO.

Awareness of the GVSI and the Blueprint

In 2012, the launch of the Blueprint 1.0 intended to unify the visions of institutions involved in global vaccine pharmacovigilance activities and foster collaboration to increase vaccine safety worldwide through an overarching framework. Seven years later, this document now shapes global discourse. Over 75% of non-industry stakeholders interviewed had familiarity with both the Blueprint 1.0 and GVSI. In contrast, however, more than 25% of industry stakeholders reported that they had little to no familiarity with the Blueprint 1.0 and GVSI, perhaps indicating a lack of sufficient engagement with the private sector.



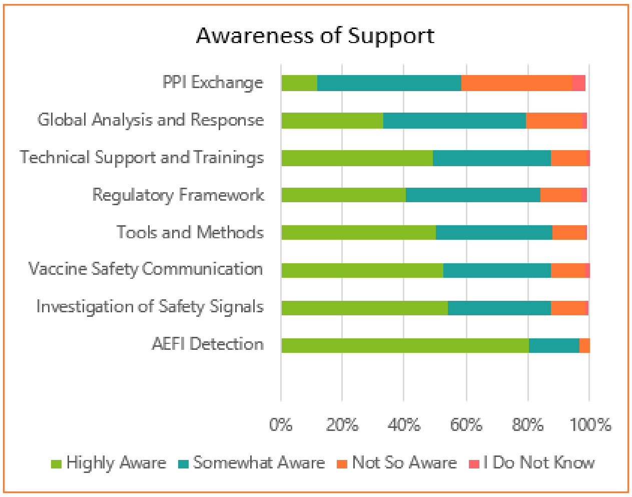
Respondents view the GVSI's overarching role in the vaccine landscape as improving vaccine safety monitoring and pharmacovigilance globally, serving as the global coordinator and convener around vaccine safety, assisting LMICs with vaccine safety systems and strengthening national capacity for vaccine safety. Non-industry stakeholders with greater familiarity with Blueprint 1.0 and the GVSI saw the role of the GVSI as the implementer of the Blueprint Strategy.

Respondents from all stakeholder groups identified the following as the primary focus of the GVSI and Blueprint 1.0:

- assisting countries with surveillance and AEFI detection through monitoring, capacity building and PV
- developing and standardizing of AEFI tools and methods
- regulatory framework / guidance / policy
- AEFI investigation
- facilitating collaboration and information-sharing

Notably, non-industry stakeholders placed greater emphasis on analysing global vaccine safety trends, while industry emphasized training and technical support.

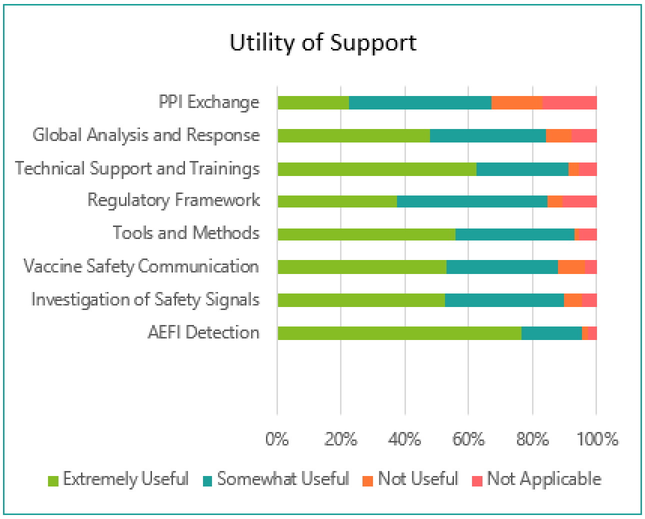
These results align with the perceptions of support for the eight strategic objectives outlined by Blueprint 1.0.



Stakeholders were most aware of the objectives that related directly to adverse events – AEFI detection (96%), investigation of safety signals (88%), and internationally harmonized tools and methods (88%). Over 80% of respondents were aware of support for six out of the eight objectives. Of the eight strategic objectives, both non-industry and industry stakeholders have the least awareness of support for public-private information (PPI) exchange systems, expert global analysis and response, multi-level regulatory frameworks, and vaccine safety communication.

Section II: Current State of Vaccine Safety

Utility of the GVSI and the Blueprint



More than 80% of all stakeholders view the support for all but one objective as at least somewhat useful. Strengthening AEFI detection and providing technical support and trainings were viewed as extremely useful by more than 60% of respondents. In accordance with stakeholders' level of awareness, PPI exchange systems, expert global analysis and response, multi-level regulatory frameworks and vaccine safety communication had the least utility.

The perception of utility derived from the implementation of these strategies at the field level.

> *The work of the GACVS, for example, has impact as it reaches a global audience and some of [its] output…is useful for decision-making in both pre and post-market settings. Thus,* ***usefulness depends not only on what WHO produces but also on whether countries adopt and implement the work products or act on the advice/guidance provided by WHO or WHO-affiliated committees.***
>
> -National Regulatory Staff

> *Thanks to GVSI for the great work done over the years in achieving its 2020 goals. There is however need to address gaps identified, such as* ***maternal immunization vaccine safety initiatives****.*
>
> -National Regulatory Staff

Many respondents noted that the lack of materials available in Spanish, French, and Portuguese presented another challenge in the utility of the Blueprint 1.0 resources.

In terms of methods of transmitting information, respondents found the following GVSI activities useful:

- E-learning tools and trainings (22%)
- AEFI Guidelines, Rate Sheets, and Case Definitions (22%)
- AEFI detection and investigation of safety signals (18%)
- vaccine safety communication materials (16%)
- technical assistance (14%)
- investigation training (14%)
- regional conferences and data sharing (6%)

Respondents were also asked about their overall experience with materials and technical assistance provided by the GVSI.

89%	Of respondents were satisfied with technical assistance
91%	Of respondents were satisfied with standards and best practices
93%	Of respondents would like to see more materials

These materials can be in the form of more technical support and training, regularly updated tools and guidance, and regular sharing of information back to countries. The most frequent examples of topics for future materials include crisis communication plans and other materials for safety communications, setting up functional AEFI committees, materials to assess causal relationships and safety signals, risk management materials, communication materials focused on vaccine hesitancy, and guidance regarding monitoring vaccine safety in pregnant women.

Respondents noted a few areas in particular for future trainings and technical support as well – these include epidemiological safety assessment, regulatory training and safety signal identification. They also mentioned that guidance is needed in the areas of patient compensation and causality assessment.

Section II: Current State of Vaccine Safety

Key Successes and Challenges of the Blueprint

Interviewees were asked about what they view as key successes and challenges of Blueprint 1.0. Recurrent themes with respect to the greatest successes include:

1. establishment of a framework of **priorities** and objectives for those in vaccine safety
2. increased **awareness of vaccine safety** that led to standing up safety programs in many LMICs and a benchmark for those countries
3. increased **capacity in LMICs** from GVSI trainings, setting up national AEFI committees, and forums to bring together EPI, regulators, and other staff
4. increased **harmonization of reporting**

> *The Blueprint was really important in my activities because it provides the vision for growth of vaccine safety implementation in my country. I also developed indicators based off the Blueprint that have proven very helpful.*
>
> -National Regulatory Staff

> *The Blueprint was a very important global effort to try to systematize our approach, sensitize stakeholders, and increase ownership.*
>
> -Academia

When asked about challenges of the Blueprint, interviewees mentioned **dissemination and implementation** of the various materials created by the GVSI, and the need for a **better communications strategy,** so that people understand what has been done to determine the safety of vaccines and why a particular vaccine is considered safe. Additionally, LMICs still struggle with **safety monitoring of new vaccines**, and regulators in LMICs need more expertise to evaluate the safety of novel products. Respondents continued to point to **limited collaboration** between national regulatory agencies and EPI, the need for **country ownership of harmonization**, and the **politicization of immunization** that has led to challenges not just for perceived vaccine safety but also vaccine use more broadly.

Not limited to the Blueprint, limited resources were noted as recurring challenges. As countries are asked to do more, there is a cost in both financial and human terms. **Signal detection, workforce training, causality assessment, and active pharmacovigilance** also remain broader challenges for vaccine safety. Many barriers to active surveillance in LMICs are still prevalent, from harmonization of records to quality of data, but participants noted a desire for a global network of sentinel centres and more joint multi-country studies as a step to building a global evidence base.

Case Studies of Vaccine Safety

This report includes the case studies of HPV and rotavirus vaccines as contrasting examples of vaccine introduction, reception and response.

Both case studies included in this report demonstrate the importance of strong **post-marketing surveillance system to support evidence-based communication to the public**. In the case of rotavirus, the pre-clinical trials were not sufficiently powered to help understand the risk, but post-marketing surveillance and enhanced AEFI detection empowered regulators, manufacturers, and the public by quantifying the risk and allowing them to make informed decisions about where to roll out vaccines by using the epidemiology of rotavirus itself. Post-marketing surveillance was essential to understanding and communicating the risk-benefit case of these vaccines.

The HPV vaccine case study exemplifies why safety data are so important amidst vaccine hesitancy. In many countries, the HPV vaccine has faced rumours of adverse events and severe reactions. Armed with comprehensive safety data, countries and manufacturers have been able to create communications strategies demonstrating the proven safety of the vaccines to increase the public's vaccine confidence.

Rotavirus

Balancing vaccine safety and efficacy can be difficult, as exemplified by the case of rotavirus. Rotavirus vaccines protect children under five from rotavirus gastroenteritis[1], averting approximately 28,000 deaths per year, but rotavirus vaccines also present a unique safety issue. When the first rotavirus vaccine, RotaShield, was introduced for routine immunization of American infants in 1998, it got withdrawn within a year due to risk of intussusception in the two weeks that followed vaccination.[2] In the United States of America, where the rotavirus infection does not lead to as significant a burden as in developing countries, the estimated risk of intussusception at 1 excess case per 10,000 vaccinees posed too high a risk for adverse events. The adverse events following the widespread post-licensure use of rotavirus vaccines demonstrate the importance of enhanced detection – particularly through the use of sentinel surveillance – during vaccine introductory periods, facilitated by an understanding of local epidemiology for risk-benefit monitoring and post-marketing surveillance to quantify the risk of adverse events.

United States

Before licensing the second generation of rotavirus vaccines, RotaTeq and Rotarix, manufacturers conducted large clinical trials in more than 60,000 children without observing an increased risk for intussusception.[3] After other countries reported an increased risk during post-marketing studies, the United States conducted a Mini-Sentinel safety assessment with the largest general population cohort for vaccine safety surveillance in that country. The study found a 1.5 excess case of intussusception per 100,000 recipients for RotaTeq.[4] The use of sentinel surveillance to quantify risk allows health officials to make more informed decisions in the promotion of rotavirus vaccination.

Mexico

In 2006, Mexico began mass vaccination with Rotarix, preceded by decades of effort documenting the burden of the disease, most notably a longitudinal study of rotavirus infection in the 1990s. Within just two years, diarrhoea mortality declined by 41% among infants in Mexico and by 46% among all children under five years of age.[5] Two post-licensure surveillance studies completed in 2011 and 2012 found a short-term low-risk of intussusception of approximately 1-4 excess cases out of 100,000 vaccinated infants in comparison to a baseline rate of 38-88 cases per 100,0000 infants.[67] Evaluation of rotavirus vaccine safety and effectiveness and a thorough understanding of rotavirus epidemiology in the Mexican context significantly contributed to sustained vaccine use and decreased prevalence of rotavirus.[8]

India

Nearly a quarter of under-five diarrhoeal deaths globally occur in India.[9] In 2016, India established an active surveillance system when it introduced domestically produced rotavirus vaccines as part of the Universal Immunisation Programme. Controversy ensued regarding the vaccine's efficacy and safety, given that the clinical trials of that product enrolled 6,800 participants in contrast to the 70,000 participants in the Rotarix vaccine clinical trials, that the phase III clinical trial showed only 56% efficacy.[10] Currently, at least two national sentinel hospital networks conduct active surveillance of intussusception and rotavirus disease to further assess the risk-benefit profile of these novel rotavirus vaccines.[11]

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[1] https://jamanetwork.com/journals/jamapediatrics/fullarticle/2696431

[2] https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html

[3] https://www.fda.gov/vaccines-blood-biologics/biologics-post-market-activities/two-fda-cber-mini-sentinel-studies-completed-safety-gardasil-and-rotavirus-vaccines

[4] https://www.nejm.org/doi/full/10.1056/NEJMoa1303164

[5] https://academic.oup.com/cid/article/56/4/548/352600

[6] https://www.nejm.org/doi/full/10.1056/NEJMoa1012952

[7] https://www.ncbi.nlm.nih.gov/pubmed/22695189

[8] https://academic.oup.com/cid/article/56/4/548/352600

[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3761026/

[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3761026/

[11] https://bmjopen.bmj.com/content/9/4/e024840

Section II: Current State of Vaccine Safety

Human Papillomavirus (HPV)

Several respondents cited the HPV vaccine when asked about increases in perceived concern about vaccine safety and limited uptake of vaccines. First introduced in 2006, the adjuvanted quadrivalent HPV vaccine has now been adopted in over 100 countries for adolescent immunization programs, with over 270 million doses distributed as of June 2017. Post-licensure surveillance data have detected no serious safety issues to date, except rare reports of anaphylaxis and regular review by the Global Advisory Committee on Vaccine Safety (GACVS) has not identified any safety concerns.[12] However, despite proven safety and robust scientific evidence of the vaccine's benefits in decreasing viral prevalence and cancerous pathologies, the seeds of scepticism have impacted uptake globally. Uganda, Denmark, Ireland, Japan, China, Colombia, Brazil, and Niger have all exhibited waves of vaccine hesitancy, demonstrating the erosion of public trust in both HICs and LMICs. These examples demonstrate the **importance of educating target populations, including adolescents, parents, and health professionals, and ensuring robust pharmacovigilance, through rapid signal detection and causality assessment**, to investigate AEFIs before they shape a nation's perceptions of a vaccine.

Denmark

Denmark benefited greatly from the introduction of the HPV vaccine until media reports contesting vaccine safety resulted in a 50% drop in vaccination coverage since 2014. In 2016, the Danish Health Authority surveyed parents to understand the root of their concerns. They launched the "Stop HPV, Stop Cervical Cancer" which leveraged print and social media, particularly Facebook, to build vaccine confidence and provide parents with safety data addressing specific concerns to promote informed opinions. Just a year after the campaign, the number of girls participating in the HPV vaccination program had doubled.[13]

Japan

Starting in April 2013, Japan launched the national HPV immunization program for female adolescents between 12 and 16 years of age.[14] Sensational news reports surfaced within weeks of AEFIs, including chronic pain and motor impairment, which resulted in the suspension of the recommendation to vaccinate. The vaccine has remained available on the market. The vaccination rate among young women has dropped to less than 1% from its peak at 70% in 2013. Currently, vaccinated individuals seeking damages for alleged side effects have brought class action lawsuits against two vaccine producers and the health ministry.[15] The recommendation for vaccination has not been reactivated, despite several studies disproving any association between HPV and reported adverse events, underlining the impact of government and media on public perception of vaccine safety.

Uganda

Given a cervical cancer incidence almost three times the global average, Ugandan officials exhibit great urgency in having a successful HPV immunization program. However, the introduction of the HPV vaccine in Uganda suffered from the association with sexually transmitted infections and a bottleneck in information dissemination.[16] While these initial fears have been assuaged with information campaigns in schools, the precarity of vaccine perception must be safeguarded by building up pharmacovigilance capacity.

> “*[We need] innovative proactive education and user-friendly media communication of vaccine safety information from kindergarten to primary schools, then secondary school to adults. Our HPV vaccine candidates are our future guardians for vaccinees of their children!*
>
> -National Regulatory Staff”

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[12] https://www.who.int/vaccine_safety/initiative/tools/HPV_vaccine_rates_information_sheet_1217.pdf?ua=1

[13] https://www.who.int/features/2018/hpv-vaccination-denmark/en/

[14] https://www.tandfonline.com/doi/full/10.1080/14760584.2019.1584040?scroll=top&needAccess=true

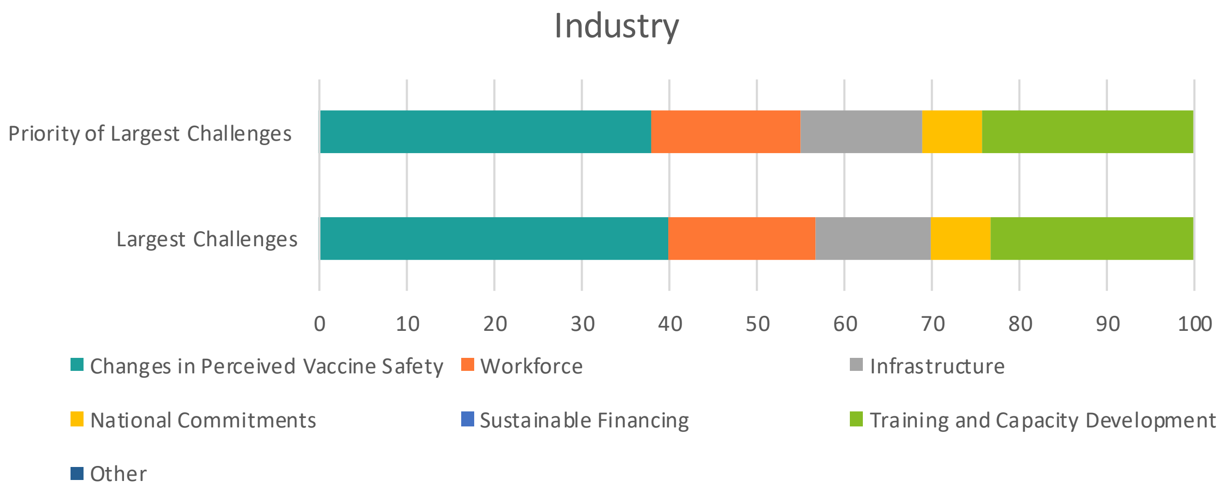
[15] https://www.sciencemag.org/news/2019/03/japanese-court-rules-against-journalist-hpv-vaccine-defamation-case

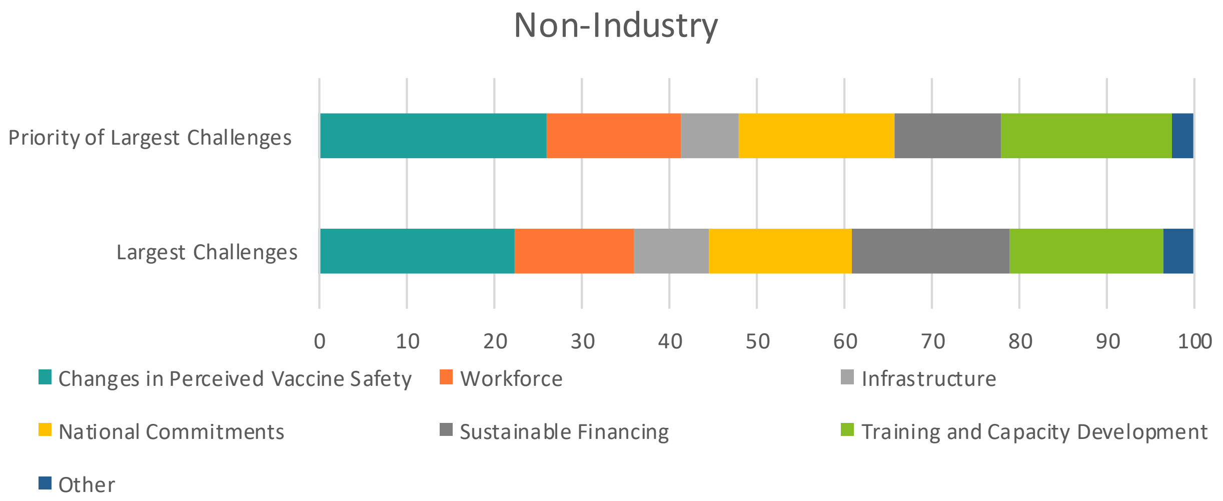
[16] https://clintonhealthaccess.org/lessons-learned-uganda-delivering-hpv-vaccines-hard-reach-girls/

Section III: Future State of Vaccine Safety

Challenges and Threats to Vaccine Safety

As the Immunization Agenda 2030 and Blueprint 2.0 are developed, it is important to take stock of the broader challenges with respect to immunization and vaccine safety. To that end, all stakeholders were asked what they view as the greatest challenges and threats facing vaccine safety in today's landscape.





The greatest challenges identified by non-industry respondents in order of priority were changes in perceived vaccine safety, training and capacity development, national commitments, workforce, and sustainable financing. Industry respondents prioritize the same first two challenges – changes in perceived vaccine safety and training and capacity development. In contrast, however, they viewed infrastructure as a greater priority than national commitments – a natural difference given their positionality. Notably, no industry respondents prioritized sustainable financing while over 10% of non-industry correspondents did.

How can we combat those challenges?

Recommendations for vaccine hesitancy and perceived issues with vaccine safety

> *WHO has a key role to play [regarding changes in perceived vaccine safety]. It is in a position to monitor perceptions globally…It can* ***develop strategies and roll out plans to counter vaccine hesitancy.***
>
> -Industry

> *Better* ***tools for communication and advocacy*** *in light of increasing vaccine hesitancy.*
>
> -Academia

> *There is a need to increase publication on vaccine safety based on quality data collected in post-marketing routine and/or stimulated surveillance systems…This must* ***include media, TV, and other mass media*** *to bring to the public knowledge the safety and benefits of immunization and minimize vaccine hesitancy.*
>
> -Global Agency

> ***Set standards and strategies for countering anti-vaccine lobbies.***
>
> -Civil Society

> *One of the biggest needs in vaccine safety is communications. There is a lot shown on safety of vaccines but the general public still do not consider that vaccines are safe. It is probably because we still* ***haven't found the right way to communicate****.*
>
> -Civil Society

Vaccine Hesitancy and Vaccine Confidence

With a changing landscape of growing vaccine hesitancy and misinformation, stakeholders view this issue as one of the largest threats to vaccine safety and would like to see it addressed in Blueprint 2.0 and the GVSI's future activities.

- When asked about the largest challenges facing vaccine safety today, 22.4% of non-industry respondents selected "changes in perceived vaccine safety", the highest of any option.
- When asked about the largest challenges facing vaccine safety today, 40% of industry respondents selected "changes in perceived vaccine safety", the highest of any option.
- 24.3% of total respondents selected "addressing misinformation" as another area they would prioritize in the next decade, the highest of any option for this question.
- 75% of non-industry respondents reported seeing an increase in perceived vaccine safety concerns in the past decade and loss of public confidence in vaccines, such as misinformation spread through social media, anti-vaccine lobbyists, and other channels.*

*Note: Industry was not asked this question.

Stakeholders specializing in vaccine confidence noted that safety is often the number one issue affecting confidence. The general public does not always know how much goes into the determination of the safety of vaccines, and a single WhatsApp or social media post questioning vaccine safety can rapidly evolve into panic and hesitancy within a community. If there is a known risk, that information should be appropriately communicated so that there is preparedness for possible reactions. Some stakeholders would also like to frame the conversation in terms of vaccine confidence rather than vaccine hesitancy. To combat hesitancy, most stakeholders agreed that proactive and comprehensive communication is key. Engaging civil society, engaging religious leaders, engaging across social media – these are all important steps to building trust in vaccines. When an adverse event occurs, it is important to be responsive and notify the community of the investigation's outcomes to keep their trust.

Recommendations for increasing transparency in light of emerging outbreaks and emergency response

Stakeholders want to see increased transparency as new vaccines go to market, with risks and benefits of vaccines clearly and proactively communicated. With emerging pathogens like Ebola, stakeholders noted that that there may be a need to push vaccines to the field without comprehensive data on vaccine effectiveness and safety. In these cases, transparency and engagement become even more important.

Respondents selected **public health authorities (25.1%), health care providers (19.7%), regulatory authorities (16.3%) and media (16.3%)** as the main organizations and individuals responsible for **communicating vaccine safety risks.**

Respondents suggested **engagement of local media (19.8%), engagement of health care workers and providers (19.1%) and engagement of the general public (16.7%)** as the top ways to improve risk communications.

These responses indicate a need to conduct grassroots campaigns to train and educate communities and health providers. Without assuaging vaccine hesitancy, the execution of immunization programs is at risk, impacting vaccination rates and threatening the health of the population.

When asked about addressing safety monitoring and communication challenges particularly in crisis or emergency situations, the most common themes from all respondents were **proactive communication and coordination (31%), comprehensive risk communication strategies to include rapid response teams (24%) and increasing transparency by emphasizing the risk/benefit case (20%). In particular, 21% of industry respondents also noted collaboration with NRAs and vaccine safety advisory boards** as a critical part of addressing safety monitoring and communication challenges.

What We Heard:

How the GVSI can help increase transparency in light of emerging outbreaks and emergency response

> “***Guidance and support*** *for stronger integration of* ***vaccine benefit-risk monitoring*** *in health care system. Recommendations and support to Member States on use of electronic health databases for vaccine benefit-risk monitoring.*
> -National Regulatory Staff ”

> “*WHO needs to develop* ***new protocols/standards for accelerated approvals*** *to ensure post-marketing surveillance is built-in.*
> -Global Agency ”

> “***AEFI country risk assessment, management, and communication plans*** *in line with current social media challenges and crisis management plus consumer education on vaccine safety.*
> -National Regulatory Staff ”

> “***Develop a model for collaboration*** *between partners [e.g.,] joint outbreak or emergency response task force for the evaluation of the obtained safety data and assessment [of] potential safety signals.*
> -Industry ”

> “***Risk communication is extremely critical in emergency situations and epidemics.*** *Why could we not give a vaccine to this population? Why can we now? Important to have strong messages of safety from WHO.*
> -Civil Society ”

Section III: Future State of Vaccine Safety

Recommendations for monitoring public questioning and loss of confidence in vaccine safety

All participants suggested various forms of proactively monitoring public questioning and loss of confidence in vaccine safety to identify and combat vaccine hesitancy, with a focus on social media monitoring.

When asked about ways to monitor public questioning and/or loss of confidence in vaccines, respondents from all stakeholder types suggested **media monitoring, analysis of internet forums and social media, and reviewing vaccine coverage rates** most frequently in their responses.

Additional suggestions included **surveys and focus groups, including household surveys, other methods of community engagement, and engagement with health workers** to include documentation of reasons for non-vaccination to determine whether those reasons are related to perceptions of vaccine safety.

Why is this important?

> ***We can only have confidence if we have evidence and better risk communication.*** *… We need to develop the capacity to speak about risks without people getting scared. We need to learn to communicate with different audiences.*
>
> -National Regulatory Staff

What We Heard:

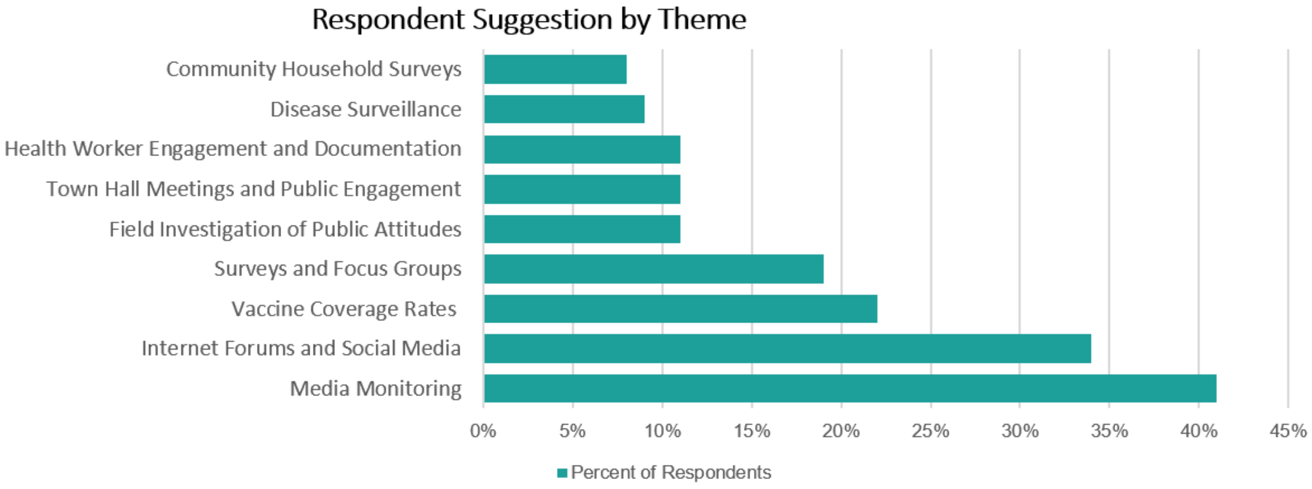
Monitoring Public Questioning and Loss of Confidence in Vaccines

> *While monitoring of mainstream media occurs this misses the entire conversation.* ***Monitoring must include in-depth social media analysis*** *and* ***ongoing surveys of key groups.***
>
> -Academia

> *By* ***establishing a database that captures confidence in vaccines*** *though regular surveys.*
>
> -National Immunization Staff

> ***Monitoring coverage/vaccine uptake*** *would be an outcome indicator;* ***Qualitative research/focus groups*** *may provide a range of identified concerns;* ***Household based surveys*** *can be used to monitor knowledge and acceptance of vaccines.*
>
> -Global Agency

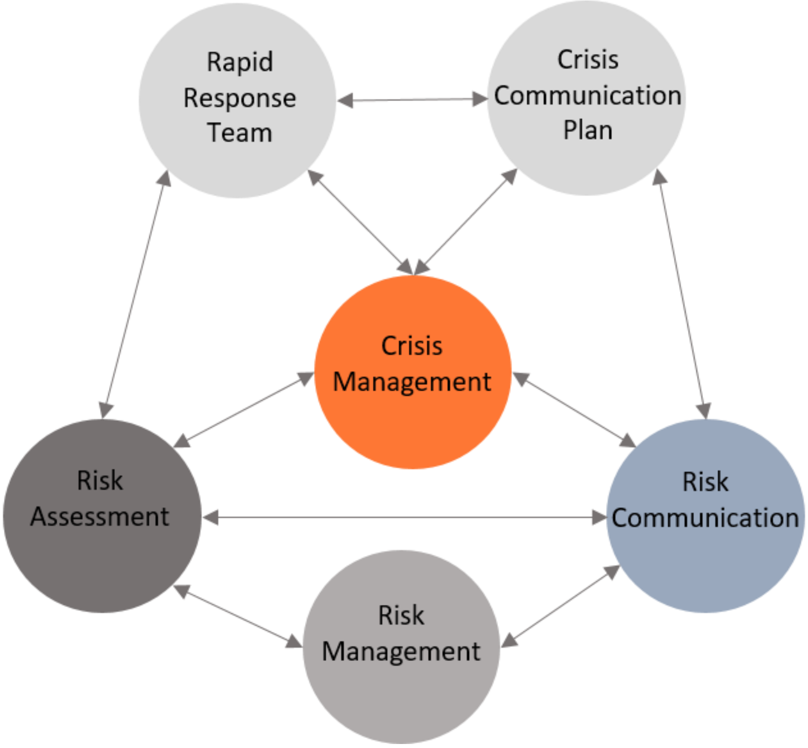
> *Through new indicators being developed by the* ***WHO Demand Data Working Group****, convened by EPI Team…*
>
> -Global Agency



Section III: Future State of Vaccine Safety

Recommendations to address other challenges to vaccine safety

Respondents would like to see proactive creation of frameworks to monitor and respond to crises quickly and effectively, with a focus on crisis communication plans and risk management.

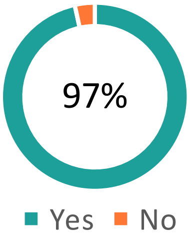


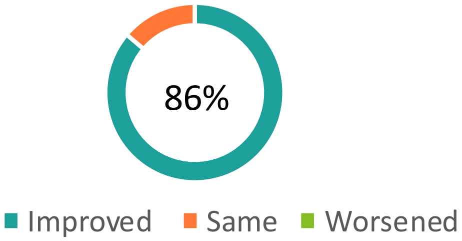
> ***Risk assessment, risk management, and risk communication*** *shall be subject for more elaborated guidance,* ***in particular for emergency vaccination programmes****, such as Ebola, Zika, or pandemic flu immunization.*
>
> -Global Agency

> *By being active on social media and other communication channels with scientifically proven and true information.* ***Rather than react to crisis situation, we must provide ALL information ahead of time.*** *I say ALL because sometimes it is the small apparently unimportant information that triggers crisis.*
>
> -Civil Society

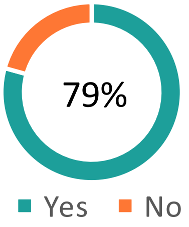
From industry stakeholders …

Manufacturers had a greater role in vaccine safety crises in last decade



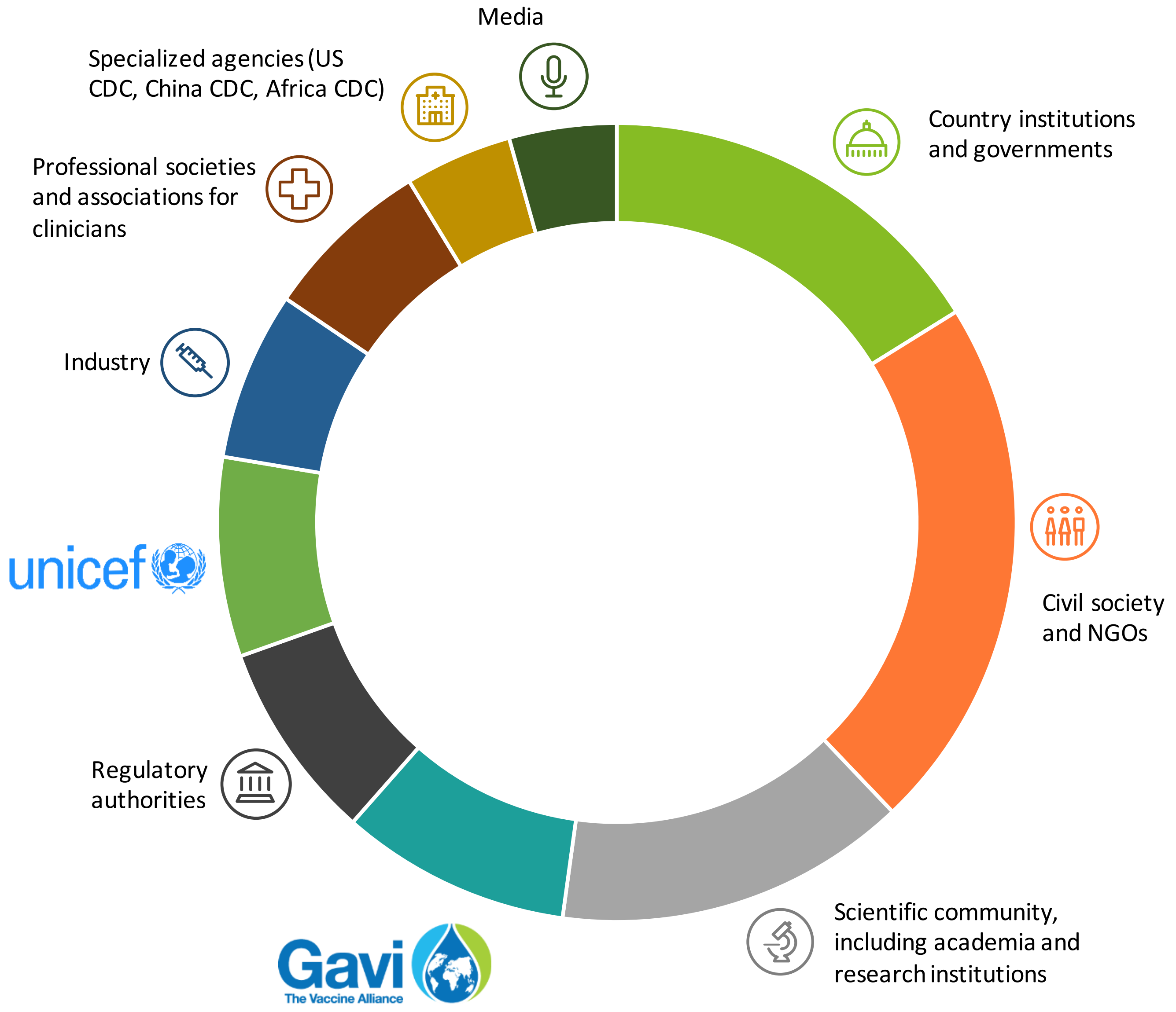


Risk management plan of products



Global crisis management improvement

Who are the key stakeholders beyond WHO for addressing the largest challenges to vaccine safety?



When asked about stakeholders other than WHO that are critical to improving vaccine safety capacity, the most common responses were civil society and NGOs, country institutions and governments, and the scientific community, including academia and research institutions.

Stakeholders also mentioned the importance of working with international agencies, such as UNICEF and Gavi, and aligning the Blueprint with the Gavi 5.0 strategy. Other stakeholders mentioned include regulatory authorities, industry, professional societies and associations, specialized agencies, and media.

Section III: Future State of Vaccine Safety

Vaccine Safety Monitoring Gaps at the Country Level

Although non-industry respondents noted that country-level capacity has seen remarkable improvement since the drafting of Blueprint 1.0, more improvements are needed, particularly in terms of the latter portions of the vaccine safety lifecycle.

Feedback/communication and causality assessment With respect to the need to build capacity post-2020, the highest proportion of respondents saw the greatest need in feedback/communication and causality assessment, at 16.8% and 15.1%, respectively."

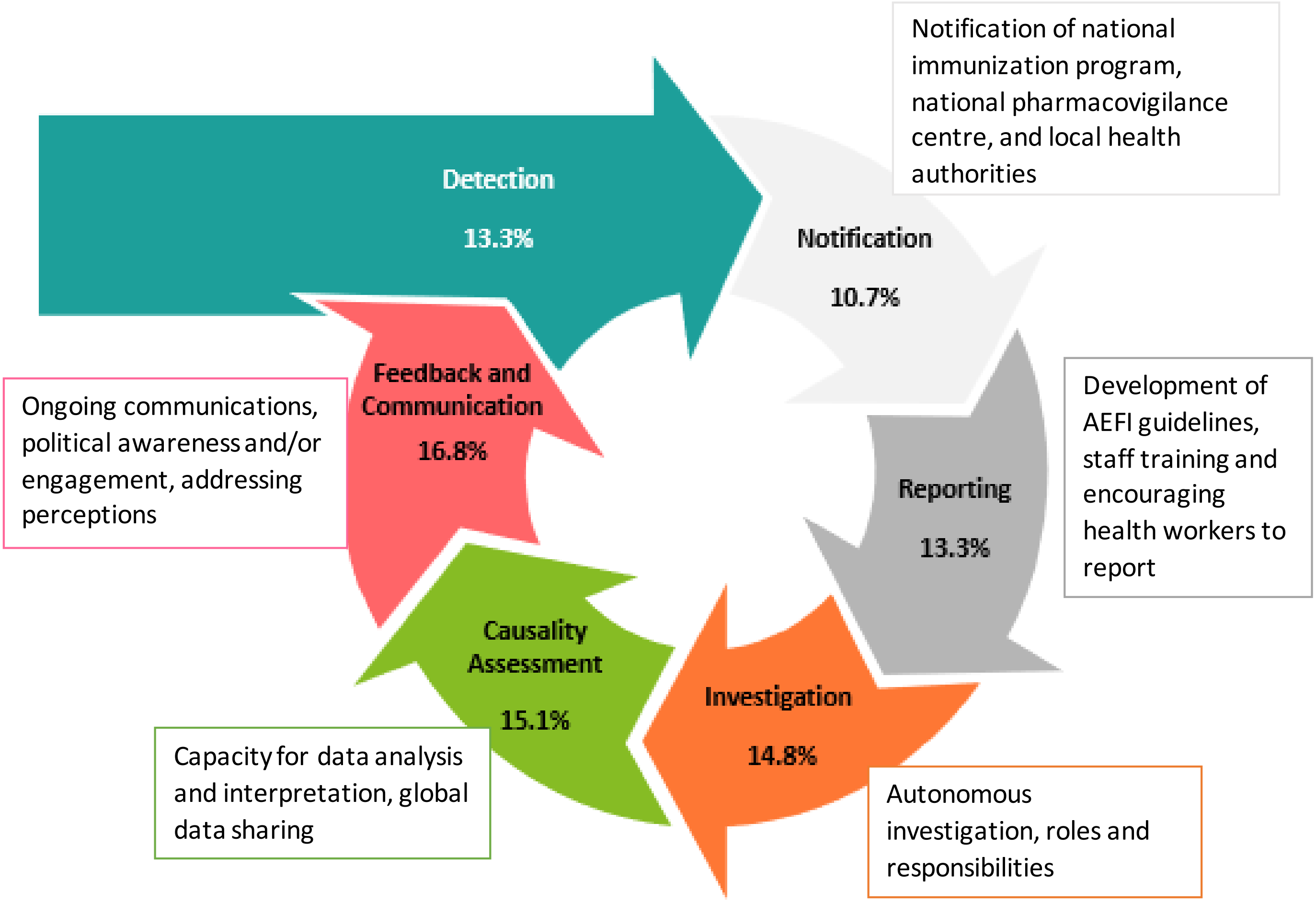
Recommendations for how to address

Specifically, stakeholders noted throughout the survey that crisis communication plans, active surveillance and causality assessment should be priorities in terms of the GVSI's technical support, training, resources and sharing of information. Additionally, some participants recommended a type of vaccine safety accreditation program that would measure capacity of vaccine safety systems and identify system gaps across the safety monitoring cycle.

For each phase of the safety monitoring cycle, respondents noted a few areas of improvement as illustrated in the following figure.

Safety Monitoring Cycle

Which areas of the safety monitoring cycle do you view as requiring additional capacity?



Notification of national immunization program, national pharmacovigilance centre, and local health authorities

Development of AEFI guidelines, staff training and encouraging health workers to report

Autonomous investigation, roles and responsibilities

Capacity for data analysis and interpretation, global data sharing

Ongoing communications, political awareness and/or engagement, addressing perceptions

Percent of total non-industry responses shown for each area of the lifecycle

Note: Industry did not receive these questions

Section III: Future State of Vaccine Safety

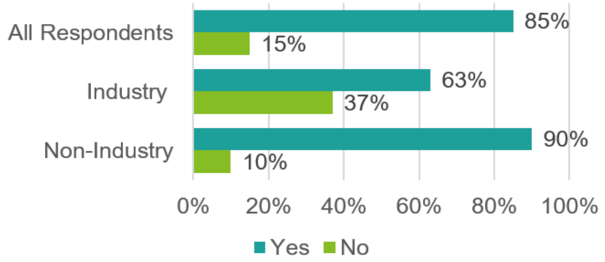
Is Harmonization Possible?

Global data-sharing platforms

Significant interest exists in regional or global platforms to share data, but both industry and non-industry stakeholders have concerns about harmonization of surveillance platforms and the investment, infrastructure, and political will harmonization would require.

Harmonization of AEFI surveillance is desired by stakeholders overall, with over 85% having an interest in internationally harmonized systems. However, industry respondents were much less interested in international harmonization, with only 63% expressing interest in harmonized surveillance compared to 90% in non-industry respondents. The most common harmonization challenges identified by respondents – funding, staffing, political will, and infrastructure/resources – are highlighted below. Additional responses included incomplete AEFI reporting, government ownership of surveillance, and competing priorities.

Interest in increased internationally harmonized active surveillance systems



Global reporting forms

While data sharing and harmonization of global platforms are critical in creating a united response, equally critical is the quantity and quality of the reporting data.

> *We have guidelines for AEFI surveillance…When we receive the reports, there is an AEFI form for serious reports, we have revised our form to be in line with the current WHO AEFI causality assessment…[then] upload the reports to the Vigibase and the country AEFI database.*
>
> -National Regulatory Staff

When asked of the utility of a universal AEFI reporting form to ensure data quality, many industry respondents noted the need for data uniformity to facilitate rapid, accurate analyses (31%). Several mentioned that the need was already filled by the existing Council for International Organizations of Medical Sciences (CIOMS) standardized International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2B form. The greatest challenges for data harmonization identified by 28% of industry respondents included different requirements, different information and different levels of infrastructure. These barriers to data quality may well impact data quantity if health professionals in the field or industry officials are unsure of how to report in a standardized way.

INVESTMENT AND FUNDING (35%)

*"If no **financial external resources are mobilized** and if no **national political willingness** can be obtained to assume a new challenge with financial obligations, it will be very hard to push this Initiative in the way that we wish".*

-Global Agency

WORKFORCE/TRAINED STAFF (21%)

*"Unless the system is well understood and used by health workers at lower levels, there will be a gross underestimation of reports. Hence governments and partners should allocate enough resources to establish a dedicated system and **train health workers on the importance of reporting.**"*

-Health Professional

POLITICAL WILL AND COMMITMENT (26%)

*"As we have a common goal in managing vaccine safety, there should be **a higher degree in transparency and willingness** to share data between the parties."*

-Industry

INFRASTRUCTURE AND RESOURCES (18%)
(INCLUDING INFORMATION PLATFORMS)

*"[There are] Different platforms collecting the same information which are not speaking to each other. There is **lack of commitment to integrate surveillance platform from countries**. The fact that the information has different data sources …countries will never own and account for the results."*

-Regional Immunization Staff

Recommendations for how to address harmonization

- *Raise awareness and increase use of WHO's standardized AEFI reporting forms by governments and industry.*
- *Create an international platform that uses the standard form template for data entry and analysis.*
- *Facilitate public-private coordination during new vaccine campaigns when populations are most vulnerable to AEFIs.*

How Can Industry Support Global and National Vaccine Safety?

Across all respondents, the survey found a desire for more participation and collaboration from industry in pharmacovigilance at a national and global level.

Current methods for reporting and causality assessment

Overall, industry views itself as playing a critical role in reporting and investigating adverse events. Indeed, 93% of industry respondents reported that their organization has dedicated and trained staff responsible for pharmacovigilance. In reporting adverse events, industry most commonly viewed its role as reporting to national authorities and/or WHO for serious AEs, investigating the adverse event, gathering information, conducting a medical and causality assessment, managing information regarding safety to guide potential actions related to risk/benefits and ensuring compliance with all regulations, laws and guidelines.

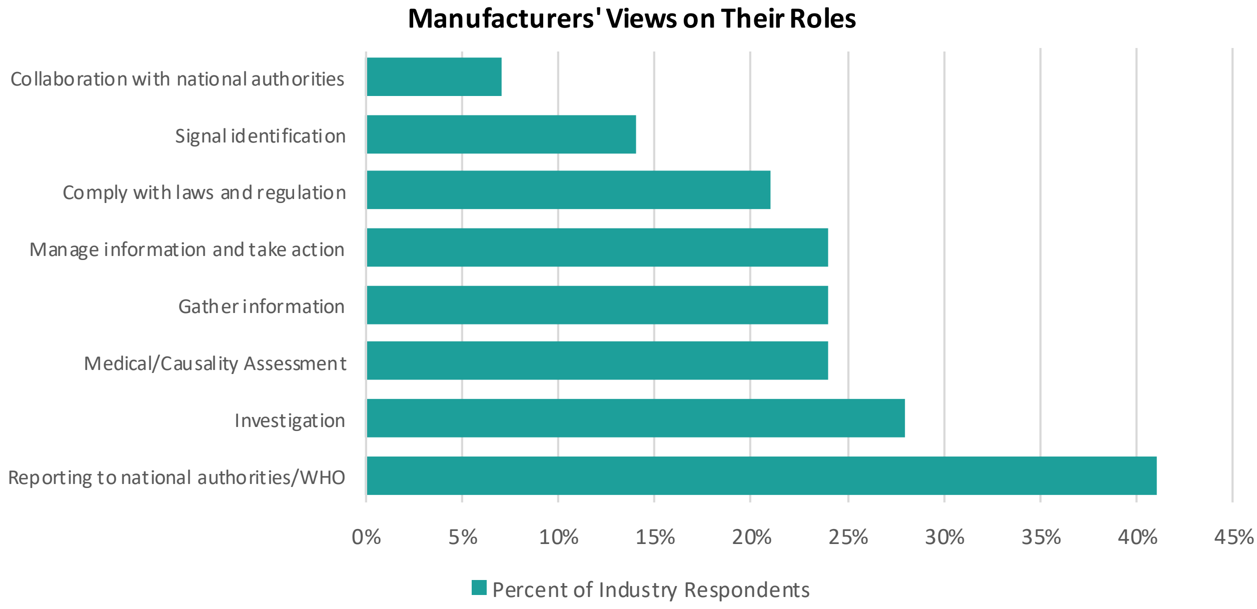
When describing their current methods for conducting causality assessments, over 45% reporting using WHO tools or guidance, followed by 17% following the company's standard operating procedures or processes.

Improvements for Periodic Benefit-Risk Evaluation Reports and other aspects

To improve reporting of Periodic Benefit-Risk Evaluation Reports (PBRER), industry wants to see more training/workshops (17%), less redundancy and individual case information (14%), mandatory implementation (14%), more data and information (10%) and data sharing with the field (10%).

Industry also expressed interest in receiving and sharing more information. In particular, over 48% of industry respondents stated that they do not currently receive information from epidemiologic studies conducted by health authorities but would like to receive that information, and over 40% stated they want to share more information with NGOs in vaccine pharmacovigilance collaborations.

To improve post-marketing surveillance, non-industry stakeholders also view industry as playing a key role in not only reporting but also funding surveillance. For example, 59% of non-industry respondents believe that industry should fund post-marketing surveillance of their products. However, many who noted the importance of this role also emphasized that steps must be taken, such as pooling industry resources, to prevent any conflict.



Section IV: Future State of the GVSI and the Blueprint

Revisiting Existing Strategic Objectives

While respondents noted the value of all of the current Blueprint strategic objectives, they expressed recommendations to revisit some of those strategic objectives. These areas include public-private information exchange, regulatory framework, global analysis and response, and vaccine safety communication.

PPI Exchange

Only 22% of respondents found the GVSI's support of public-private information exchange extremely useful, with over **10% finding it not useful at all.** Both industry and non-industry respondents noted that they want more **timely and consistent information-sharing** between those two groups, with WHO serving as the convener to do this.

Regulatory Framework

Only 36% of respondents found GVSI's support for a regulatory framework extremely useful. **Industry** respondents in particular noted that they view **WHO as playing a critical role to assist regulatory bodies** with setting up frameworks.

Global Analysis and Response

Over 20% of respondents view global analysis and response as a primary focus for the GVSI. However, **8% of respondents found the GVSI's support of global analysis and response not useful at this time.** Many respondents noted that **WHO can fill critical data analysis gaps regarding adverse events** and serve as a "trusted source of information" for vaccine safety information and analysis of global trends.

Vaccine Safety Communication

The survey found that **18%** of respondents would like to see **vaccine safety communication prioritized** in the 2030 strategy. Many respondents noted that **the WHO communication materials are theoretical and need more practical examples**, particularly considering the changing landscape. They also emphasized the importance of **implementing communication strategies before vaccine introduction** to educate the population on the vaccine safety profile in advance of immunization roll-out.

> "*I think vaccine safety communication* ***needs to be revisited*** *seriously…* -Global Agency"

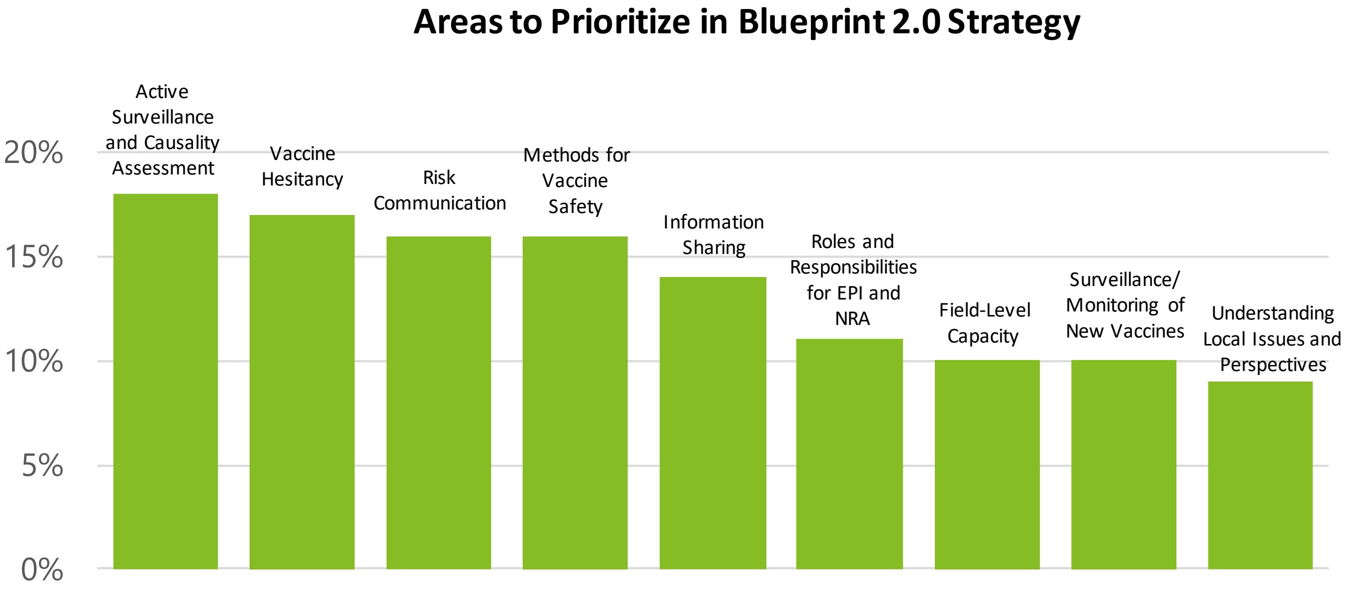
Considering New Strategic Objectives

Respondents noted a range of areas to prioritize in the 2030 strategy, from **including local perspectives** to **active surveillance and causality assessment** to **outlining roles and responsibilities** for different stakeholders. Some stakeholders also noted a need for vaccine safety guidelines in conflict, civil disorder, and emergency/low-resourced settings as well as guidelines for monitoring vaccine safety for pregnant women. Stakeholders also cautioned WHO to take on only a small number of priorities to maximize impact.

Industry respondents included many of the same areas to prioritize in the 2030 strategy but the most common themes were **building field-level capacity, public-private partnerships, and improving coordination with adverse drug reaction stakeholders and frameworks**.

> "***Develop transparent partnership[s]*** *with other stakeholders in Pharmacovigilance* ***like the pharma industry and NGOs****. Help the LMIC to develop their own national database compatible with Vigibase.* -Industry"

> "*There is a communication section but probably also need* ***an advocacy stream of work to develop political will*** *to build effective AEFI surveillance and response systems.* -Global Agency"



The Need for an Accountability Framework

In both the survey responses and the interviews, respondents highlighted the importance of measurement and evaluation of Blueprint 2.0's strategies and activities. As part of the development of the next Blueprint, **the GVSI can utilize an accountability framework to measure its implementation progress over the next decade.** These measures can align closely with the accountability framework set forth in the upcoming Immunization Agenda 2030 and previously in the GVAP (https://www.who.int/immunization/global_vaccine_action_plan/GVAP_Annex6.pdf).

To best track and measure progress, both in communicating to stakeholders and to identify points for real-time program improvements, the accountability framework could be applied to:

- monitoring results (defined as progress against Blueprint 2.0's Goals and Strategic Objectives);
- documenting and monitoring GVSI stakeholder commitments and participation
- tracking resources (and use of resources) invested in monitoring and managing AEFIs
- harmonization and interoperability of vaccine safety data systems and use of regional-level data for decision-making

Stakeholders mentioned collecting data on feedback mechanisms, case reports, safety-related signals, dedicated resources to pharmacovigilance, national immunization Technical Advisory Groups, committee for causality assessment, monitoring capacity, and regulatory process to measure vaccine safety capacity.

> ***GVSI needs to quantify the accomplishments in some way.*** *Lots of important work has been done, but how do we measure what has been achieved? What is the impact?* -National Regulatory Staff

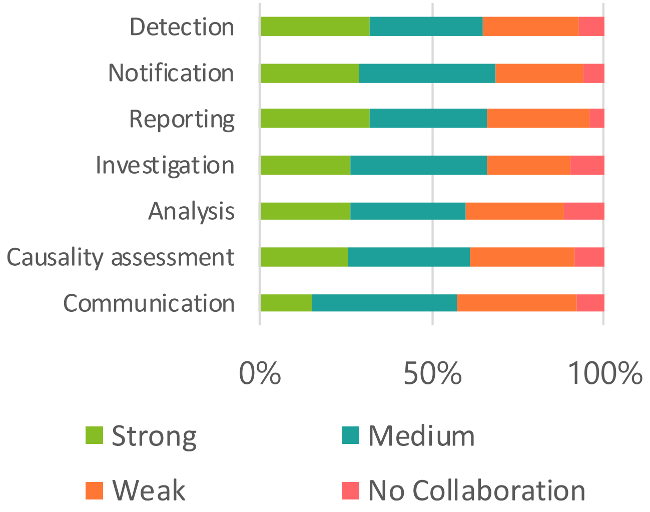
> ***Monitoring and evaluation is key*** *so that there is optimal use of resources and all players contribute to resource mobilization and government support for success of these initiatives I think.* -National Regulatory Staff

Section V: Vaccine Safety Ecosystem

Collaboration

Many respondents noted collaboration challenges in country, particularly between EPI and NRAs and with the private sector, as well as a lack of channels to share data and information.

Perceived Levels of Collaboration between EPI, NRAs, Industry, and NGOs

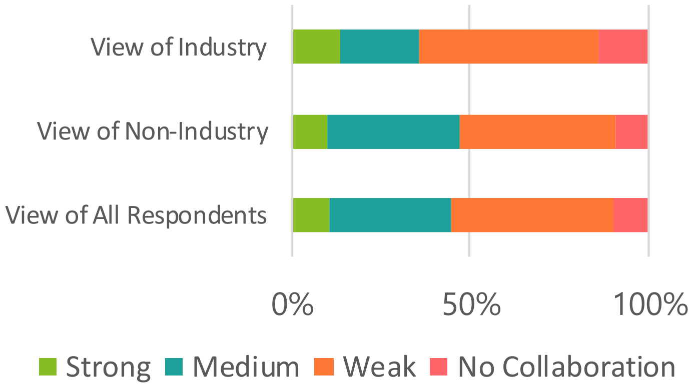


Collaboration challenges noted by respondents include:

- challenges between **regulators and immunization programs** (20%)
- limited collaboration with **manufacturers** (19%)
- coordination (16%)
- conflict of interest perceptions with manufacturer-funded research (12%)
- roles and responsibilities, including turf issues (12%)
- lack of trust (8%)

The largest **difference between industry and non-industry respondents is in the area of collaboration with respect to communication**, with only 10% of non-industry respondents viewing it as strong while 35% of industry respondents viewed it as strong. Discrepancies between industry and non-industry stakeholders are also evident in the categories of investigation and detection.

Perceived Levels of Collaboration between Countries



Collaboration challenges noted by respondents include:

- lack of **regional collaboration** (24%)
- limited **mechanisms to share data** (16%)
- limited **communication regarding vaccine risks and misinformation** (12%)

Industry respondents were more likely than non-industry respondents to characterize collaboration between countries as "weak" (50% compared to 43%)

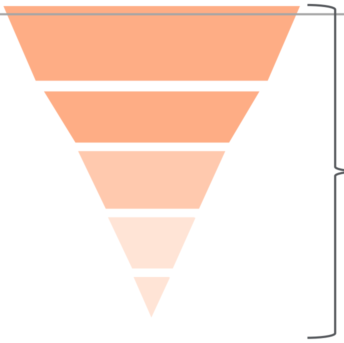
> *I've been surprised by the complexity of collaboration in vaccine safety, since all stakeholders want optimal pharmacovigilance. Instead of trying to get every thinkable stakeholder under one approach, we should try to change the mindset. We should* ***encourage stakeholders to be transparent and proactively communicate****, rather than waiting for a request for information.*
>
> -Industry

To improve collaboration, stakeholders suggested creating an electronic platform to quickly share trusted information with healthcare professionals. Some stakeholders also mentioned that consortiums could be useful to allow more rapid and comprehensive sharing of information, particularly with industry.

Section V: Vaccine Safety Ecosystem

Roles and Responsibilities at Different Levels

	Responsibilities	Needs	What We Heard
Global	• Convening and coordination • Global analysis and response	• Global monitoring and evaluation • Outlining roles and responsibilities to enable collaboration • Standardization and guidelines	*“**Building systems so that data can be interpreted and communicated**. Can also help give guidance to countries on how to create structures in-country that facilitate communication.”*
Regional	• Expert committees • Regional conferences	• Creation and standardization of data-sharing platforms • Provision of technical assistance • Financial and human resources	*“… facilitate ability of **countries with less capacity to work in collaboration with the stronger countries in the region** and benefit from that experience (assess data collectively).”*
National and Subnational	• Maintain PV through regulatory authorities • Manage national immunization and vaccination programs	• Guidance on crisis and risk communication • Capacity building for minimal standards with AEFI reporting and investigation	*“To **build capacity to recognize and investigate AEFI** and identify areas where **training and education can be effectively implemented**”*
Field	• Provide care and disseminate information • Conduct vaccinations	• Training of local staff on signal detection, including procedures for passive and active surveillance • Communicate the importance of reporting and use of AEFI tools	*“Unless the system is well understood and used by health workers at lower levels, there will be a gross underestimation of reports. Hence governments and partners **should train health workers on the importance of reporting.”***
Community	• Understand and promote herd immunity	• Transparency from governments and industry • Media monitoring to address vaccine hesitancy	*“**Involve communities [and] empower them with correct information**. Inform communities of avenues to reach in case of doubt. “*



Industry

Industry has a **role to play at each level** in **monitoring the safety of their products** and **sharing that information** with respective stakeholders.

Section V: Vaccine Safety Ecosystem

Roles and Responsibilities

Role of WHO

Both industry and non-industry stakeholders view WHO as playing an essential and singular role as the **"lead", "catalyst", and "global messenger"** for vaccine safety. **Advocacy with governments for funding and political will** appeared as the most frequent theme in terms of the GVSI's role in addressing vaccine safety challenges, with 25% of respondents mentioning this area. Other frequent themes mentioned by respondents regarding the GVSI's role in addressing challenges include the following:

- Set standards and guidance as well as conduct training
- Communicate and share experiences with in-country staff
- Coordinate and convene
- Support countries
- Lead with innovative approaches and solutions
- Facilitate data sharing between different groups
- Enable self-financing of national PV systems and improved self-reliance with respect to allocation of resources
- Global monitoring and evaluation

Role of global partners

Global partner respondents see themselves largely as funders and advocates to advance the work of WHO and other partners and advocate for an increased focus on vaccine safety at the country level. These partners play a role in strengthening the pharmacovigilance of both national regulatory bodies as well as industry. Some partners are also playing a role in building a global information base by assisting with AEFI surveillance, signal detection and other areas critical to vaccine safety and assisting with technical guidance and harmonization of reporting forms.

Role of regional bodies

Stakeholders view the role of regional bodies and regional support as critical to improving country-level capacity. Regional groups provide technical assistance through financial resources, human resources, and guidance and can liaise between global agencies, donors and countries regarding concerns, global initiatives and important communications. Regional bodies are often more aware of country needs and challenges than are global bodies, so they can ensure that country-level needs are being addressed and communicated as needed.

Regions can also serve as a hub for sharing best practices between countries of all income levels, and many respondents noted the value of creating regional platforms for data sharing. Many respondents also noted the value of regional ITAGs and other expert committees and meetings to advise on vaccine safety and disseminate information, and even suggested the creation of regional GACVS bodies to work with national AEFI committees.

> "*WHO Regional offices have a key role in advocacy for vaccine safety, provision of technical assistance to assess performance and improve national systems, setting regional and sub-regional platforms for exchange, learning and addressing particular sub-regional challenges;*
> -Global Agency"

Role of academia, experts, and researchers

Respondents from academia, vaccine safety experts, and researchers view their role mainly as building, assessing, and synthesizing the evidence base for vaccine safety. Some academic bodies have created groups focused on vaccine hesitancy and other rising issues, and many experts can provide expert review of causality assessment, epidemiologic studies and other aspects of vaccine safety. Experts from academia and research can also provide technical support and assist with building infrastructure and supporting the workforce of the national immunization program, but they also noted **that political will is critical for this to be achieved**. External stakeholders can play a role only if government bodies have clearly delineated roles and responsibilities of each party.

Role of industry

In building a vaccine safety system, industry sees its own role mostly as one of information-sharing, coordination and transparency. Industry also views its role as providing technical and operational support to governments and regulatory authorities in particular, assisting with capacity building and training, conducting pharmacovigilance and post-marketing surveillance on their own and ensuring they are following guidelines, maintaining quality control and meeting regulatory obligations.

Other stakeholders view much of industry's role in the same way – information-sharing, coordination, and transparency were also the most common themes respondents flagged as major roles for industry. However, other non-industry stakeholders put higher value on industry conducting pharmacovigilance and post-marketing surveillance of their own, AEFI reporting, accountability and liability for their products, and funding/resources. In fact, **58% of non-industry respondents noted that manufacturers should fund post-marketing surveillance**.

Role of NRAs

Regulator respondents viewed their role in the vaccine safety system as primarily an enforcer of tailored post-marketing surveillance and AEFI reporting. Other frequent themes among regulators included coordinating the vaccine safety system; contributing, monitoring and implementing a response to AEFIs; leading the vaccine safety system; and sharing information with manufacturers as well as AEFI program staff and experts.

Other stakeholders viewed regulators in a similar light, highlighting regulators' role as the coordinator of the vaccine safety system most frequently, but also noting information-sharing and contributing, monitoring, and implementing an AEFI response. Other stakeholders also noted the importance of regulators playing a role in strengthening the vaccine safety system and setting up its infrastructure, as well as conducting training and increasing awareness around vaccine safety.

Role of immunization programs

Stakeholders agree that immunization programs have an essential role to play in early detection and response to safety issues using AEFI surveillance. These programs can also assist with epidemiologic studies and causality assessments if the resources and capacity are available. These programs are the ones leading implementation of immunization in the field, and thus must identify current gaps in vaccine safety as well as train health workers and immunization staff in the field to detect and report any adverse events. Many respondents also noted the importance of timely communication and sharing of information with regulatory authorities to conduct and maintain pharmacovigilance.

Role of field level staff

Throughout their survey responses participants highlighted **the importance of improving understanding of processes and impact at the field level among health workers** in the community.

> *We have to **train health care workers in a different way**. They are often not given information they need, which leads to AEs. We need to really help people who do the work understand why their participation is so important (and how vaccines work in reality).”*
>
> -Academia

> *The question for me is **how do we build strength and capacity from the vaccination site/clinic**? How do we **reach out to healthcare workers at these sites to train them on surveillance and AEFI reporting**? We have seen there have not been enough resources to get training down to clinic level.*
>
> -National Regulatory Staff

Role of media

Respondents emphasized the growing importance of proactively engaging traditional and nontraditional media outlets as perceived vaccine hesitancy grows.

Role of the public

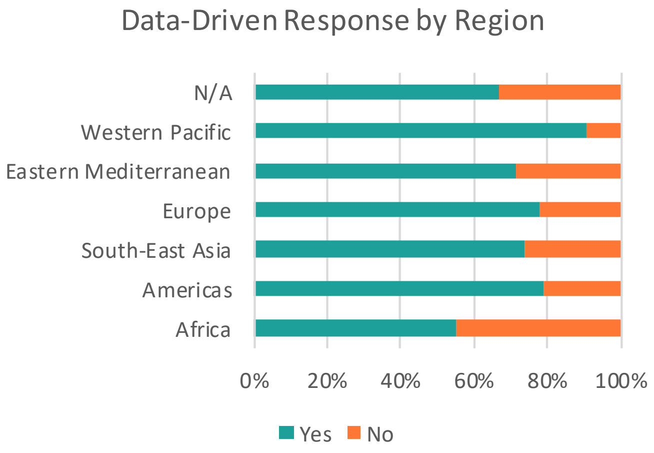
As vaccine hesitancy grows, respondents agree that vaccine safety information must be proactively communicated so that risks and benefits are clear to the public. This communication should be done in alignment with broader messaging around immunizations.

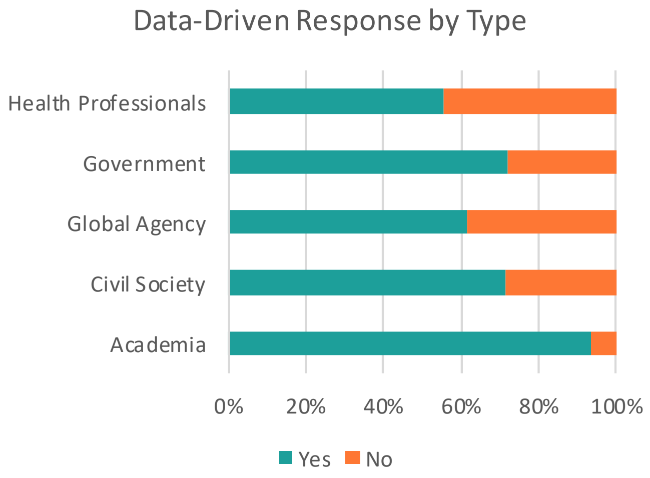
Section V: Vaccine Safety Ecosystem

Enabling Vaccine Safety Stakeholders

Data-Driven Decision Making

Data play a critical role in ensuring vaccine safety and allowing stakeholders to make informed decisions. The empowerment of actors from the field to the global level requires accurate and updated data dissemination. A greater percentage of industry stakeholders reported reviewing safety data daily or weekly compared to non-industry stakeholders (14.5%, 16.5%). More than 70% of all stakeholders responded that they had used data in decision-making. There were notable variations in non-industry responses when broken out by region and profession:





In the regional breakdown, while the majority of non-industry respondents from all regions noted using data in decision-making, only 55% of stakeholders from the Africa and less than 80% of stakeholders in five out of six other regions responded affirmatively. In the breakdown by type, global agencies (61.5%) and health professionals (55.6%) had the smallest percentage of respondents indicating that they used data-driven decision-making.

The most commonly cited (>10%) sources for decision-making for all respondents included:

- information and guidelines from WHO
- information and guidelines shared by national government bodies
- information from expert clinician groups
- manufacturer reports and communications
- reports from vaccine safety groups

Respondents also noted that media reports as well as research and scientific journals are used for decision-making in their roles.

To better support general decision-making related to vaccine safety, non-industry stakeholders identified the following factors: better data and information; access to country, regional and global data sources; training and technical support for AEFI signal detection; real-time information on new vaccines and changes in vaccine policy, and coordination and communication. They overwhelmingly identified WHO as the entity best equipped to provide that support, underscoring the importance of WHO leadership in global vaccine safety.

> “*[We need] tools, data for reporting AEFI. Ethicists who help us think through the population level benefit versus individual risk. Communicators who know how to translate technical knowledge into digestible information for the public that will increase vaccine confidence.*
> -Academia ”

> “*A major challenge is when I have the data, what do I do with it? We need the competence in country for data analytics and interpretation.*
> -National Regulatory Staff ”

How can the GVSI support these stakeholders?

The GVSI can continue to support vaccine safety stakeholders, not only by sharing information but also through other means. Respondents most commonly mentioned the following when asked how the GVSI could better support the vaccine capacity of their country or organization:

- more training of local staff in vaccine safety signal detection, including passive and active surveillance (27%)
- information-sharing related to AEFIs with global partners, academia, and country staff (19%)
- assistance with development of AEFI report collection, analysis, and guidance (15%)
- establishing collaborative partnerships (12%)
- working with regional and national technical advisory committees and other regional meetings (11%)
- ensuring countries have the capacity to disseminate vaccine information (11%)
- providing regional level support, including financial and human resources (8%)

> *We need the evidence base to communicate, or the tools to look for evidence. This is the only way that I can tell the population that I have the best evidence and make decisions based off of this evidence. This is a critical part of our role in pharmacovigilance.*
>
> -National Regulatory Staff

information-sharing appears as a theme again and again – sharing between stakeholders in country, in regions, and globally. In the next decade, WHO and its partners can continue to enable more timely and transparent data sharing for vaccine safety. Stakeholders also proposed innovative sharing mechanisms such as a vaccine safety app with up-to-date resources and information, and WhatsApp or other messaging groups for regional pharmacovigilance stakeholders.

How can GVSI enable country ownership?

Respondents also noted many ways that GVSI can further enable country ownership in the next Blueprint 2.0 and over the course of the next decade of activities. Many suggestions fell within the following themes:

- support information and data sharing globally, between countries, and provide data to WHO to be shared with countries
- support countries in the development of surveillance and a comprehensive vaccine safety system
- advocate and educate local stakeholders on the process and impact of vaccine safety monitoring
- conduct training and education
- training to empower countries to tailor and drive their own approach
- engage countries in decision-making meetings and GVSI workshops focused on ownership

There were also mentions of opportunities to benchmark country progress towards vaccine safety ownership as part of evaluating their maturity level.

> *Providing technical assistance to strengthen the institutional capacities, to develop and implement strategies to build and increase human capacity resources and ensure financial resources in order to ensure sustainability of the AEFI surveillance system…*
>
> -Global Agency

> *Advocacy. Country-ownership will occur in the extent that vaccine safety surveillance becomes recognized as an integral component of national immunization programs, with a dedicated budget, sufficient staff, operating procedures and monitoring of performance dictated by the national public health authority.*
>
> -National Regulatory Staff

Section VI: Conclusions

As the World Health Organization shapes Immunization Agenda 2030, over 200 global vaccine safety stakeholders reviewed the impact of vaccine safety priorities and activities over the past decade, capacity improvements made and still needed, as well as the role of rising vaccine hesitancy and emergencies in the context of vaccine safety.

This background research revealed a large improvement in vaccine safety capacity since the initial Blueprint 1.0, but many of the same gaps remain, and stakeholders offered ideas about how to build a roadmap for the next decade that includes new priorities, increased ownership and collaboration, and accountability.

Emerging Vaccine Safety Themes

Many respondents noted new challenges that have evolved over the past decade, from the rise of vaccine hesitancy to maintaining surveillance and pharmacovigilance in crises, emerging outbreaks and other emergencies. A few areas of focus that had not been addressed in Blueprint 1.0 include:

- vaccine safety in the context of **vaccine hesitancy and misinformation**
- transparency during **emerging outbreaks and other emergencies**, including accelerated protocols and monitoring of new vaccines
- **crisis management and risk management**
- Post-marketing surveillance in **conflict**, **civil disorders and low-resourced settings**

Persisting Vaccine Safety Themes

Overall, the findings of this research align closely with many of the findings from the initial landscape analysis conducted in 2012 prior to Blueprint 1.0, as they constitute the perennial challenges for global vaccine safety.

When surveying LMIC immunization managers in 2012, the main needs expressed were training and harmonized methods. That research also highlighted a need to enhance sharing within and across countries, as well as to improve the quality of vaccine safety data. Immunization staff noted limited collaboration and standardization between EPI and NRAs, and a lack of formal vaccine safety communication plans in place. Respondents in 2019 noted quite a few improvements across these areas, ranging from training provided, the presence of international forums convened by the GVSI to facilitate collaboration and share information, and the existence of communication strategies and plans. However, these continue to be areas where improvements can be made.

In the 2012 survey of regulators from the Post-Marketing Surveillance (PMS) Network countries, respondents frequently mentioned the need for active surveillance and causality assessment of AEFI as well as a desire for more information-sharing between countries (a theme also noted by immunization managers). One challenge noted particularly among health workers for LMICs to report AEFIs was the fear of being blamed for adverse events, leading to underreporting. Regulators also addressed obstacles to creating a global vaccine safety support structure and global harmonization for surveillance, with funding, political will, and clear guidelines as challenges for both setting up the global system and harmonizing across countries. Additional challenges noted for harmonization include conflicts of interest, compatible reporting systems, public-private partnerships and confidentiality.

Section VI: Conclusions

Finally, industry respondents noted many of the same themes in 2012 and 2019. First, they expressed a desire for clear, up-to-date, and utilized pharmacovigilance regulations, as well as clear roles and responsibilities in the vaccine safety surveillance system. Echoing immunization managers, industry respondents also highlighted the importance of educating health care professionals and health workers to improve the quality of AEFI reporting in the field.

The key findings of this research are included below, alongside the evidence base for those conclusions. The icons note whether the conclusion arose from the online survey, interviews, and/or the literature.

🖱 **Online Survey** 🗣 **Interviews** 📄 **Literature**

Conclusion	🖱	🗣	📄
Current State			
Participants are largely familiar with the goals outlined in the Blueprint 1.0 Strategy, as well as the purpose of the GVSI.	✓	✓	
Participants find resources, tools and trainings from the GVSI generally useful – the challenge remains with implementation at field level.	✓	✓	
Since the launch of the Blueprint and the GVSI, stakeholders agree that huge improvements have been made to build the minimal vaccine safety capacity of LMICs, but many of the same gaps remain – for example, active surveillance, clear roles and responsibilities, and more information-sharing between countries.	✓	✓	✓
The majority of stakeholders expressed a need for communication materials and tools to provide guidance and create greater standardization for global and in-country responses to AEFIs.	✓	✓	
Future State of Vaccine Safety			
Stakeholders view a changing landscape of growing vaccine hesitancy and misinformation as one of the largest threats to vaccine safety and would like to see this addressed in Blueprint 2.0 and the GVSI's future activities.	✓	✓	
Stakeholders want to see increased transparency as new vaccines go to market, with risks and benefits of vaccines clearly and proactively communicated.	✓	✓	
Respondents would like to see proactive creation of frameworks to monitor and respond to crises quickly and effectively, with a focus on crisis communication plans and risk management.	✓		✓
Although non-industry respondents noted that country-level capacity has seen remarkable improvement since the drafting of Blueprint 1.0, more improvements are needed, particularly in terms of the latter portions of the vaccine safety monitoring cycle.	✓	✓	
There is significant interest in regional or global platforms to share data, but both industry and non-industry stakeholders have concerns about harmonization of surveillance platforms and the investment, infrastructure and political will harmonization would require.	✓	✓	✓

Section VI: Conclusions

Conclusion	🖱	🗣	🗐
Future State of the GVSI and the Blueprint			
Respondents find all objectives laid out in Blueprint 1.0 as critical aspects of maintaining pharmacovigilance and improving vaccine safety capacity globally. However, there are a few areas, particularly public-private information exchange and vaccine safety communication, which in the next Blueprint may want to revisit to ensure utility of implementation activities. Some stakeholders also recommended that Blueprint 2.0 select a few key areas to maximize impact in the next decade.	✓	✓	
There are new areas that participants would like to see prioritized in the next Blueprint. Respondents from all stakeholder types want to see strategies to address vaccine hesitancy; further development of vaccine safety methods, particularly for evaluation and monitoring of new vaccines; guidance related to maternal immunization; and more incorporation of field perspectives. Industry also wants to see prioritization of field-level capacity, public-private partnerships, and increased coordination with respect to pharmacovigilance. Respondents also noted the importance of active surveillance and causality assessment, and the delineation of roles/responsibilities for EPI and NRAs.	✓	✓	
Notably, stakeholders called for a greater focus on country ownership in Blueprint 2.0 and an accountability framework to measure and evaluate progress towards desired objectives.	✓	✓	
Vaccine Safety Ecosystem			
Stakeholders identified a range of collaboration challenges. Collaboration between countries is still viewed by over 50% of respondents as weak or nonexistent, particularly in low and middle-income countries. In country, collaboration faces obstacles from tensions between regulators and immunization programs, sharing of information with manufacturers, and conflict of interest perceptions that limit that collaboration.	✓	✓	✓
To improve collaboration, many respondents noted the need to more clearly define the roles and responsibilities of each stakeholders, from field-level health workers to global players, and to improve communication channels between these groups.	✓	✓	✓

The Global Vaccine Safety Blueprint 2.0 is an opportunity to refocus global efforts on several key priorities in this changing landscape of immunization, enable regional, national, and local stakeholders to own pharmacovigilance and collaborate with increased transparency, and measure the substantial progress that has been made. With these changes, WHO and its partners can continue towards the vision set forth in the Blueprint --- a world with effective vaccine pharmacovigilance systems established in all countries.

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Appendix

Appendix

Methods for Analysis

In order to support the Global Advisory Committee on Vaccine Safety in the development of Immunization Agenda 2030, Deloitte conducted a stakeholder assessment to provide recommendations on future vaccine safety priorities and to ensure that Blueprint 2.0 and the Global Vaccine Safety Initiative (GVSI) address the rapidly changing world of immunization in its future efforts.

Two surveys were distributed. Survey 1 encompassed all non-industry stakeholders and included a section on vaccine safety capacity at the organizational level. Survey 2 included four of the five sections from Survey 1 but replaced the organizational capacity section with an industry-specific section on pharmacovigilance for manufacturers. Interviews were then conducted over telephone for a subset of respondents to get their views.

Survey and Interview Tools

Survey 1

Survey 2

Master Interview Guide

Components of the Research

Review the current landscape of vaccine safety and assess how the GVSI has been delivering against Blueprint 1.0 in the eyes of its stakeholders.

- Perform environmental assessment of emerging trends in vaccine safety, vaccines, and immunizations more broadly.
- Conduct stakeholder assessment identifying vaccine safety needs and potential opportunities for Blueprint 2.0.

Review the Blueprint 1.0's Strategic Objectives and assess whether priorities and activities will need to be adapted in Blueprint 2.0

- Develop recommendations on which areas may need to be prioritized in the Blueprint 2.0 strategy based on need.
- Identify opportunities for collaboration with stakeholders across the vaccine safety ecosystem.

Quantitative Analysis

The programming language R was used to create a robust analysis of both non-industry and industry respondents. For certain questions where more detail was required, the responses were stratified by region and stakeholder type.

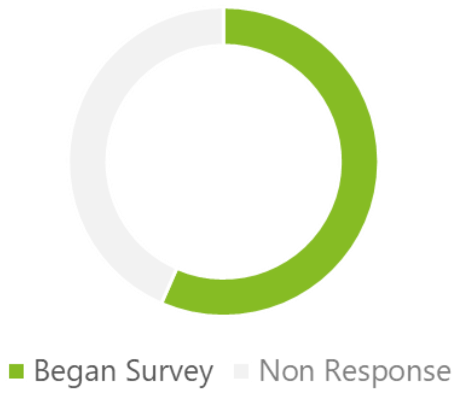
Qualitative Analysis

Two members of the Deloitte team independently coded qualitative responses in Excel and cross-checked for final analysis. Salient quotes were selected from the responses based on eloquence and relevant representation of qualitative responses.

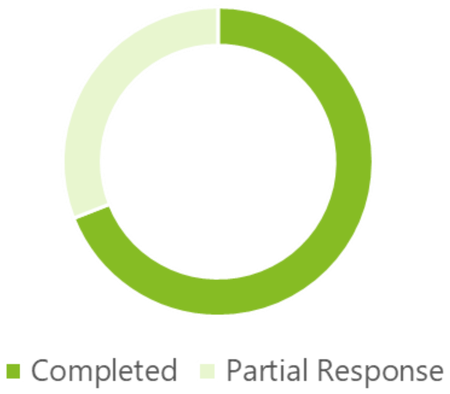
Appendix

Respondent Breakdown

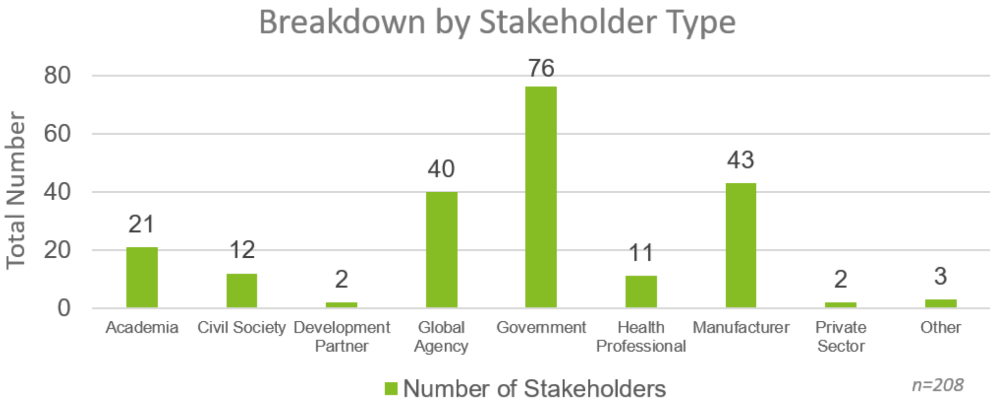
Of the **352 individuals** who received survey 1 and survey 2, 208 **(59%)** began their respective survey.



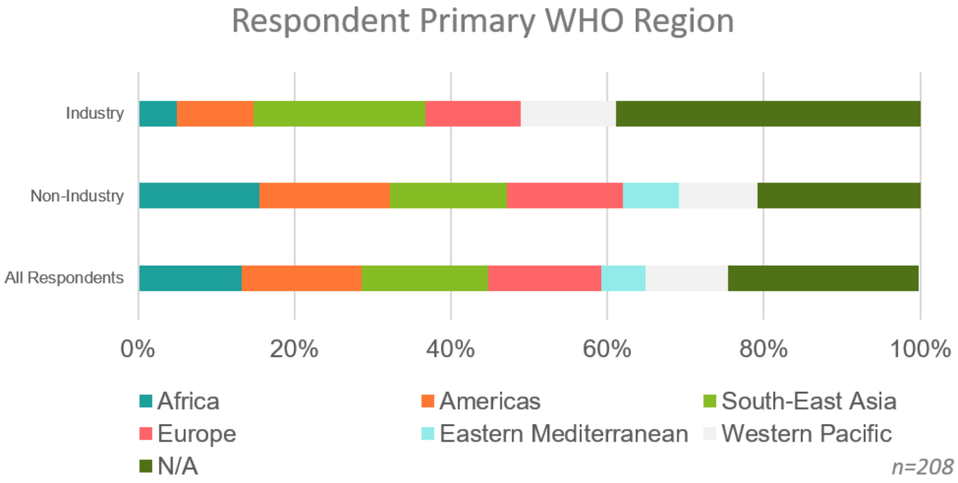
Of the **208 respondents** who began survey 1 and 2, 148 **(71%)** fully completed their respective survey.



The **largest stakeholder type** represented was government, followed by industry and global agencies.



WHO regions represented overall were South-East Asia (SEARO), followed by the Americas (AMRO/PAHO) and Europe (EURO).



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